Recommendations for the Use of Antiretroviral Drugs in Pregnant Women with HIV Infection and Interventions to Reduce Perinatal HIV Transmission in the United States

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Appendix D: Dolutegravir Counseling Guide for Health Care Providers (Last updated December 12, 2019; last reviewed December 12, 2019)

This counseling guide represents the most recent guidance by the Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission (the Panel) based on all currently available data. It replaces all prior statements regarding the safety of dolutegravir (DTG) in pregnant women and women who are trying to conceive.

Use of Dolutegravir in Pregnant Women and Women Who Are Trying to Conceive[a]

In 2018, preliminary data from a study in Botswana identified an increased risk of infant neural tube defects (NTDs) in women who were taking DTG when they became pregnant. This observation led numerous organizations, including the Panel, to advise avoiding the use DTG in women who are trying to conceive or who are already in the first trimester[b] of pregnancy. In July 2019, the results from an analysis of NTDs in a larger number of pregnancies were published. The updated data showed that the risk of infant NTDs is lower than previously reported in preliminary data, but there was still a small but significant increase in the risk of infant NTDs among women who were taking DTG when they became pregnant compared to women who conceived on a regimen that did not contain DTG. An increased risk of infant NTDs has not been found in women who initiate DTG during pregnancy.

Because updated data indicate that the increased risk of NTDs associated with the use of DTG is small, and because DTG has the advantages of once-daily dosing, being generally well tolerated, and producing rapid, durable viral load suppression, which is important for the prevention of perinatal HIV transmission, **the Panel now recommends DTG as a *Preferred* antiretroviral (ARV) drug throughout pregnancy, and as an *Alternative* ARV drug in women who are trying to conceive**. The Panel strongly recommends that use of DTG be accompanied by appropriate counseling to allow patients and their health care providers to make joint decisions about treatment. This counseling guide summarizes considerations that should be addressed when counseling pregnant women and women who are trying to conceive about the use of DTG. For more information, see Updated Guidance about the Use of Dolutegravir in Pregnancy in Recommendations for Use of Antiretroviral Drugs During Pregnancy, Table 4, Table 5, and Pregnant Women Living with HIV Who Are Currently Receiving Antiretroviral Therapy.

General Counseling Considerations for Pregnant Women and Women Who Are Trying to Conceive

- In the United States, the background risk of NTDs in the general population is 0.07% (7 per 10,000 pregnancies). The Centers for Disease Control and Prevention (CDC) notes that 3,000 pregnancies are affected by infant NTDs every year in the United States.
- DTG exposure at the time of conception was associated with a small but significant increase in the risk of infant NTDs in a birth surveillance study in Botswana. The prevalence of infant NTDs was slightly higher in women who were taking DTG at the time of conception (0.30%, or 30 infants with NTDs per 10,000 deliveries) than in women without HIV infection (0.08%, 8 infants with NTDs per 10,000 deliveries) or in women who initiated DTG later in pregnancy (0.03%, 3 infants with NTDs per 10,000 deliveries). The risk of infant NTDs was higher in women who were taking DTG at the time of conception than in women who were receiving efavirenz (EFV)-based antiretroviral therapy (ART) at the time of conception (0.05%, or 5 infants with NTDs per 10,000 deliveries).
- Although data have not shown an increase in the risk of NTDs in infants born to women who initiated DTG during pregnancy, it is important to note that there is a background risk of NTDs regardless of the ART regimen used or a woman's HIV status. With the exception of EFV, there are not enough data to determine the risk of NTDs with periconception use of any of the other currently *Preferred* and

Alternative ARV drugs in the United States. Using the data from Botswana, we can now rule out a three-fold or more increased risk of NTDs associated with periconception use of EFV.

- Before, during, and after pregnancy, clinicians and patients should discuss future childbearing desires and plans, the potential risks and benefits of conceiving while taking specific ARV medications, including DTG, and contraceptive options to prevent unintended pregnancy.
- Folic acid is known to lower the risk of NTDs in the general population. The United States Public Health Service recommends that all pregnant women and women who might conceive take at least 400 mcg of folic acid daily and continue to do so throughout pregnancy. Unlike food in Botswana, food in the United States is routinely fortified with folate. However, there is no established link between the use of DTG and impaired folate metabolism, nor is there any evidence that folate supplementation prevents NTDs that are associated with the use of DTG.
- It is important to help women weigh the available information about the risks of NTDs when using DTG against what is known (or not known) about risks of NTDs associated with other ARV drugs that are recommended for use in pregnancy. To date, systematic birth surveillance data in a sufficiently large number of women to rule out an association between periconception drug exposure and NTDs are available only for EFV, which the Panel recommends as an *Alternative* ARV drug for pregnant women and women who are trying to conceive (see Table 4, Table 5, and Efavirenz).
- It is important to help women consider the available information about other potential risks associated with the use of ARV drugs, such as other birth defects or other adverse pregnancy outcomes (e.g., preterm delivery); see Teratogenicity and Combination Antiretroviral Drug Regimens and Maternal and Neonatal Outcomes for more information.
- Most NTDs occur before the neural tube closes at 4 weeks post-conception, approximately 6 weeks post-last menstrual period, often before a woman realizes she is pregnant. After 6 weeks gestation, the additional risk of NTDs developing is thought to be much less likely.
- Changes in antiretroviral therapy (ART) during pregnancy can lead to increases in viral load that increase the risk of perinatal HIV transmission; this viral rebound may affect choices for future ARV regimens due to the possible development of resistance.
- Pregnant women who are receiving DTG and present to care during the first trimester[b] and women who are trying to conceive should receive counseling about the risks and benefits of continuing DTG or switching to another ARV regimen, as described above. In most cases, the Panel recommends **continuation** of DTG for pregnant women, because:
  - The risk of NTDs is small; *and*
  - Rapid, durable viral load suppression in pregnancy is important to prevent perinatal HIV transmission, and changes in ART may result in loss of viral suppression.
- When assessing the the benefits and risks of switching a patient from DTG to another ARV drug, clinicians and patients should consider factors such as the feasibility of switching to another ARV drug, each drug's tolerability, the ability to maintain viral suppression, the risk of perinatal HIV transmission, and the risk of NTDs.
- Women who are trying to conceive should receive information about the use of specific ARV regimens, including those containing DTG; this will enable them to make informed decisions about ARV regimens before they become pregnant.
- All cases of ARV drug exposure during pregnancy should be reported to the Antiretroviral Pregnancy Registry.

Other Antiretroviral Drugs That Are Recommended for Use in Pregnancy

- Other *Preferred* ARV drug options for women who are initiating ART while pregnant or while trying to conceive include raltegravir,[c] atazanavir/ritonavir, and darunavir/ritonavir. We have a moderate amount of data about pregnancy outcomes and birth defects with each of these drugs and drug combinations. While these data are reassuring, it is important to note that a rigorous, systematic birth surveillance program that includes large numbers of women with periconception exposure like in the Botswana study does not exist for these drugs. Additionally, because of mandatory food folate fortification, the overall risk of NTDs in the United States is low in the general population, and there are currently insufficient DTG periconception exposures reported to the Antiretroviral Pregnancy Registry be able to determine whether there is an increase in the risk of NTDs in the United States.
- EFV, rilpivirine, and lopinavir/ritonavir are recommended as *Alternative* ARV drug options in pregnancy. *Alternative* drugs may have more limited data on use in pregnancy than *Preferred* drugs (e.g., rilpivirine) or may be associated with more pharmacokinetic (PK), dosing, tolerability, drug interaction, or resistance concerns than those in the *Preferred* category, but they are acceptable for use in pregnancy.
- When discussing ARV drug options, it is important to point out that some ARV drugs that are recommended for use in adults and nonpregnant women are not *Preferred* or *Alternative* options for women who are pregnant or who are trying to conceive for the following reasons:
  - Not enough is known about the safety of using some ARV drugs before or during pregnancy, because studies about their use in pregnancy are limited. It is important to emphasize that a lack of data does not indicate the absence or presence of risk. It only means that we do not have all the information about all the possible effects when using these drugs during pregnancy (e.g., bictegravir and tenofovir alafenamide).
  - For some ARV drugs (e.g., cobicistat-boosted regimens), there are PK changes in pregnancy that decrease blood levels of those agents, potentially leading to loss of virologic control and an increased risk of perinatal transmission or adverse effects on maternal HIV infection. With newer ARV drugs, PK and safety data may not be available to guide dosing in pregnancy.
- Regimens that contain atazanavir/cobicistat, darunavir/cobicistat, or elvitegravir/cobicistat **are not recommended** for use in pregnant women because of PK changes that may lead to increased viral loads later in pregnancy. Health care providers should discuss whether to continue the regimen or switch to one that is recommended for use in pregnant women with patients (see Table 5 and Pregnant Women Living with HIV Who Are Currently Receiving Antiretroviral Therapy). If a regimen with PK concerns is continued, it is important that the patient follow the instructions for taking the regimen in order to optimize absorption (e.g., taking certain drugs with or without food, avoiding antacids or divalent cation-containing vitamins). Viral load should be monitored more frequently in these patients (i.e., every 1–2 months).
- If an ARV regimen is changed during pregnancy, drugs in the new regimen should be ARV drugs that are recommended for use in pregnancy (see Table 4 and Table 5) and viral load should be checked 2 to 4 weeks after the switch.
- Recommendations regarding the use of specific ARV agents or ARV regimens often change as more information on the safety, tolerability and PK changes of these drugs in pregnancy becomes available.

Footnotes

[a] Guidance on the care of pregnant women and women who are trying to conceive is also applicable to transgender and nonbinary people of childbearing potential.

[b] The first trimester is less than 14 weeks (up to 13 6/7 weeks) gestational age by last menstrual period.

[c] Raltegravir requires twice-daily dosing during pregnancy and has a lower barrier to resistance than DTG.